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<b>(21) International Application Number:</b> PCT/EP93/01099 <b>(22) International Filing Date:</b> 4 May 1993 (04.05.93)  <b>(30) Priority data:</b> 9210576.6      18 May 1992 (18.05.92)      GB 9210594.9      18 May 1992 (18.05.92)      GB 9210595.6      18 May 1992 (18.05.92)      GB  <b>(71) Applicant (for all designated States except US):</b> SMITH-KLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).  <b>(72) Inventor; and</b> <b>(75) Inventor/Applicant (for US only) :</b> FEARS, Robin, Bradshaw [GB/GB]; SmithKline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex CM19 5AD (GB).		<b>(74) Agent:</b> GIDDINGS, Peter, J.; Corporate Patents, Smith-Kline Beecham, Mundells, Welwyn Garden City (GB).  <b>(81) Designated States:</b> AU, CA, JP, KR, NZ, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>Without international search report and to be republished upon receipt of that report.</i>	
<b>(54) Title:</b> USE OF INDOLONE DERIVATIVES FOR THE TREATMENT OF MEMORY DISORDERS, SEXUAL DYS-FUNCTION AND PARKINSON'S DISEASE  <b>(57) Abstract</b>  Selective dopamine D <sub>3</sub> receptor agonists and their use in therapy, inter alia, in the treatment of memory disorders.			

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USE OF INDOLONE DERIVATIVES FOR THE TREATMENT OF MEMORY DISORDERS,  
SEXUAL DYSFUNCTION AND PARKINSON'S DISEASE

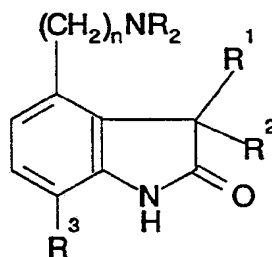
The present invention relates to the use of selective  
dopamine D<sub>3</sub> receptor agonists in therapy, for example in the  
5 treatment of memory disorders.

Compounds capable of binding selectively to dopamine D<sub>3</sub>  
receptors are known in the art (see, for example, Nature,  
1990, 347, 146). To date, however, no specific therapeutic  
10 utility has been identified for compounds having such  
properties.

The present invention resides in the identification of such  
a utility and, in a first aspect, provides selective  
15 dopamine D<sub>3</sub> receptor agonists for use in therapy.

More specifically, the present invention relates to  
selective dopamine D<sub>3</sub> receptor agonists for use in the  
treatment or prophylaxis of diseases in which agonism of the  
20 D<sub>3</sub> receptors will prove advantageous, for example, in the  
treatment of memory disorders, sexual dysfunction and  
Parkinson's disease.

Particular selective dopamine D<sub>3</sub> receptor agonists include,  
25 for example, compounds of the structure (I):



(I)

30

in which,  
each group R is the same or different and is hydrogen or  
C<sub>1-4</sub>alkyl;

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R<sup>1</sup> and R<sup>2</sup> are the same or different and are each hydrogen or C<sub>1-4</sub>alkyl; and  
n is 1 to 3,  
or a pharmaceutically acceptable salt thereof.

5

Within the scope of the structure (I) and the most preferred selective dopamine D<sub>3</sub> receptor agonist of the present invention is the compound 4-(2-di-n-propylaminoethyl)-2-(3H)-indolone hydrochloride having the INN: ropinirole.

10 The compound ropinirole and other compounds of structure (I) are known in the art, for example as having utility in the treatment of Parkinson's disease (EP 0299602-A).

The compounds of structure (I) and, in particular,  
15 ropinirole, can be prepared according to the procedures described in EP 113964-B.

Selective dopamine D<sub>3</sub> receptor agonists are of use in therapy, in particular in the treatment of memory disorders,  
20 for example, in the treatment of impaired cerebral functionality, as well as dementia, amnesia and decreased cognitive capacity; in the treatment of sexual dysfunction in both males and females, in particular in the treatment of male and female impotence; and in the treatment of  
25 Parkinson's disease.

When used in therapy, the compounds of structure (I), in particular ropinirole, are formulated into a standard pharmaceutical composition, for example as described in  
30 EP 113964-B and EP 0299602-A.

Preferably the composition is administered in unit dose form. Each dosage unit for oral administration contains preferably from 1 to 50 mg (and for parenteral  
35 administration contains preferably from 0.1 to 15 mg) of a compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base.

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The daily dosage regimen for an adult patient may be, for example, an oral dose of between 1 mg and 100 mg, preferably between 1 mg and 50 mg, or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 50 mg, preferably  
5 between 0.1 mg and 15 mg, of the compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base, the compound being administered 1 to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy.

10

#### DATA

The ability of the compounds to bind selectively to human D<sub>3</sub> dopamine receptors can be demonstrated by measuring their  
15 binding to cloned receptors. The inhibition constants ( $K_i$ ) for ropinirole displacement of [<sup>125</sup>I] iodosulpride binding to human D<sub>2</sub> and D<sub>3</sub> dopamine receptors expressed in CHO cells have been determined. Human D<sub>2</sub> receptors were obtained from Garvan Institute of Medical Research, St. Vincent's  
20 Hospital, Darlinghurst, New South Wales 2010, Australia. Human D<sub>3</sub> receptors originated from Unite de Neurobiologie et Pharmacologie (U.109) de l'INSERM, Centre Paul Broca, 2ter rue d'Alesia, 75014 Paris France (B. Giros (1991) Path. Biol. 39, 252-254). Crude cell membranes were prepared by  
25 homogenisation followed by high-speed centrifugation, and characterisation of cloned receptors achieved by radioligand binding.

#### Preparation of CHO cell membranes

30

Cell pellets were gently thawed at room temperature, and resuspended in about 20 volumes of ice-cold 50 mM Tris salts (pH 7.4 @ 37°C), 20mM EDTA, 0.2 M sucrose. The suspension was homogenised using an Ultra-Turrax at full speed for 15  
35 sec. The homogenate was centrifuged at 18,000 r.p.m for 20 min at 4°C in a Sorvall RC5C centrifuge. The membrane pellet was resuspended in ice-cold 50 mM Tris salts (pH 7.4 @ 37°C), using an Ultra-Turrax, and recentrifuged at 18,000

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r.p.m for 15 min at 4°C in a Sorvall RC5C. The membranes were washed two more times with ice-cold 50 mM Tris salts (pH 7.4 @ 37°C). The final pellet was resuspended in 50 mM Tris salts (pH 7.4 @ 37°C), and the protein content  
5 determined using bovine serum albumin as a standard (Bradford, M. M. (1976) Anal. Biochem. 72, 248-254).

#### **Binding experiments on cloned dopamine receptors**

10 Crude cell membranes were incubated with 0.1 nM [<sup>125</sup>I] iodosulpride (~2000 Ci/mmol; Amersham, U. K.), 50 mM Tris salts (pH 7.4 @ 37°C), 120 mM NaCl, 5 mM KCl, 2 mM CaCl<sub>2</sub>, 1 mM MgCl<sub>2</sub>, 0.1% (w/v) bovine serum albumin, in a total volume  
15 of 1 ml for 30 min at 37°C. Following incubation, samples were filtered using a Brandel Cell Harvester, and washed three times with ice-cold 50 mM Tris salts (pH 7.4 @ 37°C), 120 mM NaCl, 5 mM KCl, 2 mM CaCl<sub>2</sub>, 1 mM MgCl<sub>2</sub>. The radioactivity on the filters was measured using a Cobra gamma counter (Canberra Packard). Non-specific binding was  
20 defined as the radioligand binding remaining after incubation in the presence of 100 µM iodosulpride. For competition curves, 14 concentrations (half-log dilutions) of competing cold drug were used.

25 Competition curves were analysed simultaneously whenever possible using non-linear least-squares fitting procedures, capable of fitting one, two or three site models.

#### **RESULTS**

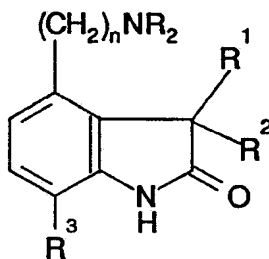
30 The binding data revealed the existence of two binding sites in both human D<sub>2</sub> and D<sub>3</sub> receptors. The inhibition constant (K<sub>i</sub>) for ropinirole at the high affinity site was found to be 1380 nM (n=5) at D<sub>2</sub> and 69.1 nM (n=6) at D<sub>3</sub> receptors.

35 These results indicate that ropinirole binds selectively (20 fold) to human D<sub>3</sub> dopamine receptors.

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## Claims:

1. A selective dopamine D<sub>3</sub> receptor agonist for use in therapy.
- 5 2. A selective dopamine D<sub>3</sub> receptor agonist for use in the manufacture of a medicament for use in the treatment of memory disorders.
- 10 3. A selective dopamine D<sub>3</sub> receptor agonist for use in the manufacture of a medicament for use in the treatment of sexual dysfunction.
4. The use according to claim 2 or claim 3 in which the  
15 selective dopamine D<sub>3</sub> receptor agonist is a compound of the structure (I):



(I)

- 20 in which,  
each group R is the same or different and is hydrogen or C<sub>1-4</sub>alkyl;  
25 R<sup>1</sup> and R<sup>2</sup> are the same or different and are each hydrogen or C<sub>1-4</sub>alkyl; and  
n is 1 to 3,  
or a pharmaceutically acceptable salt thereof.
- 30 5. The compound 4-(2-di-n-propylaminoethyl)-2-(3H)-indolone hydrochloride (INN: ropinirole) for use in the manufacture of a medicament for use in the treatment of memory disorders.

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6. The compound 4-(2-di-n-propylaminoethyl)-2-(3H)-indolone hydrochloride (INN: ropinirole) for use in the manufacture of a medicament for use in the treatment of sexual dysfunction.

5

7. The use of a selective dopamine D<sub>3</sub> receptor agonist other than a compound of structure (I) or a pharmaceutically acceptable salt thereof as described in claim 4, in the manufacture of a medicament for use in the treatment of

10 Parkinson's disease.